cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule, and wherein at least one antibody fragment comprises an antigen binding site for a polypeptide selected from the group consisting of: human vascular endothelial growth factor (VEGF), human p185 receptor-like tyrosine kinase (HER2), human CD20, human CD18, human CD11a, human IgE, human Apo-2 receptor, human tumor necrosis factor-α (TNF-α), human tissue factor (TF), human α4β7 integrin, human GPIIb-IIIa integrin, human epidermal growth factor receptor (EGFR), human CD3, and human interleukin-2 receptor α-chain (TAC).

Arguments

Claims 1-7, 9-11, 13, 15, 16, 18-24 and 26-37 (all claims pending in this application) stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner found that Applicants' arguments made in response to a similar rejection in the prior Office Action were not commensurate with the scope of the claims. Although the Examiner conceded that Haber may state that a disulfide bond is not needed for association of the heavy and light chains of an antibody, he pointed at the teaching in Haber that full reduction and carboxymethylation of antibodies has led to inactivity and that specific conformation of the heavy and light chains is necessary for binding antigen. Accordingly, according to the rejection, one skilled in the art would reasonably conclude that adding a larger molecule, e.g. a large PEG moiety would not allow the heavy and light chains to associate and to be active. From this, the Examiner concluded that undue experimentation would be required to make and use the instantly claimed antibody fragments.

The rejection focuses on the alleged lack of showing that the antibodies modified as claimed would retain "activity," i.e. the ability to bind their respective antigens. Without acquiescing in the Examiner's position, it is noted that claim 1, as currently amended, no longer requires antigen-binding, rather recites the presence of an "antigen binding site." On page 135, lines 18-28, the specification discloses reagent uses of the claimed conjugates, which include the use of the conjugate to induce tolerance for the underivatized parental antibody fragment in a test animal. In this use, the claimed conjugate serves only to prepare the test animal for use in characterizing the behavior of the underivatized parental antibody fragment free from any immune interference directed against the parental antibody fragment in the test animal. Thus, the